The Value of Mephenesin Carbamate in the Control of Pain in Patients with Tic Douloureux*

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A alleviation of the pain of tic douloureux has been attempted with many non-narcotic pharmacologic agents. Few have remained in common use for long. Vitamin B₁₂,¹²,¹³,¹⁵ hydantoin derivatives,¹⁴,¹⁷,¹⁸,¹²,¹³,¹⁴,²²,²⁴ G 32883,²,³ and mephenesin carbamate suspension⁵ have been used in recent years.

The rationale for the selection of mephenesin for this purpose was speculative. It had been noted in cats that small intravenous doses of mephenesin reduced the amplitude of the trigeminal dorsal root reflex and the overreaction to tactile facial stimulation, incident to the application of strychnine to the surface of the medulla overlying trigeminal-nucleus caudalis.¹⁰ Without great expectations, intravenous mephenesin was administered to 2 patients with severe tic douloureux. Their facial pain stopped for ½ to 1½ hours after each injection. Because of its low toxicity and the infrequency of serious side effects associated with the use of mephenesin,¹²,¹³,¹⁷,¹⁸,²¹ further efforts to control the pain of tic douloureux with this drug seemed warranted.

In 1959, we made a preliminary report describing the use of mephenesin in the management of 29 patients with tic douloureux.⁹ At the end of a one-year trial period, 10 patients reported no pain, 12 had mild pain, and 4 had moderate pain despite continuing medication. One reported no improvement. Two had been operated upon.

The present report describes the results of a 7-year study of 52 consecutive patients treated for tic douloureux with mephenesin carbamate suspension.

Clinical Material

Each of the 52 patients in this study had paroxysmal pain in the distribution of the trigeminal nerve without evidence of trigeminal deficit except for that which might be related to previous operative procedures on the trigeminal system. Trigger points were noted in all but two.

The distribution of patients by sex and age was comparable to the characteristics of the disease. Pain occurred on the left side in 27, on the right in 25 and bilaterally in 8 patients.

The duration of symptoms prior to this form of management extended for less than 1 year in 13 patients, 1–5 years in 20 patients, 5–10 years in 7 patients and for more than 10 years in 12 patients.

Twenty-three patients had had previous operative procedures in attempts to control their pain. As a result of these procedures, 8 had a mild sensory deficit, 3 had extensive sensory deficit and 1 had total anesthesia in the 2nd and 3rd divisions of the trigeminal.

Each patient was examined for lesions in the head or neck which might contribute to the production of face pain. Three patients underwent correction of dental malocclusion and others required treatment for malfitting plates or dental caries. Several patients had chronic recurrent sinusitis and 3 others had respiratory infections. X-rays of the skull were normal in each instance.

Two patients died in the course of this study, 1 after a cerebrovascular accident at the age of 74 and one at age 73 following a “heart attack.” These 2 patients had been maintained without an operative procedure for 4 and 5 years and are included as 4 and 5 year follow-ups, respectively.

Method of Management

The method of management evolved as a relatively standard pattern. Each patient was initially given 1 gm. (1 teaspoon) of mephenesin carbamate suspension every 3 hours to determine the extent of any side effects at a low dose during the next 24 hours. On the 3rd day each received 3 gm. every 3 hours. They were maintained on this dose as pain gradually subsided over a period of from 3 days to 2 weeks. On rare occasions, for periods of several days, patients received as much as 5–9 gm. every hour. Two patients received as much as 3 gms. of mephenesin carbamate every 3 hours for many months.

Twenty patients who experienced severe exacerbations and were unable to take oral medication were admitted to the hospital for
intravenous medication with mephenesin. One patient was hospitalized for this reason on 3 occasions. Four grams of mephenesin were added to 5% glucose in distilled water to a total volume of 500 cc. and this was administered by slow intravenous drip over a period of 12 hours. In several instances, 6 gm., and in one instance, 8 gm. I.V. in 12 hours, were required to control pain. The intravenous drip was maintained with a catheter for 48-72 hours. Oral medication was continued. At the termination of the intravenous medication, the patients were discharged on oral medication.

Twenty patients who experienced an exacerbation after a remission were placed also on diphenylhydantoin sodium, 100 mg., t.i.d. for brief periods. Eight have remained on both drugs for longer intervals.

When a patient no longer experienced satisfactory control of pain and was inordinately disturbed by the side effects, an operative procedure was performed.

Effect of Drug Therapy Only

For purposes of this report the success or failure of the medical management of these patients has been judged in terms of the need to resort to an operative procedure for pain control.

*Oral Mephenesin Carbamate Suspension.* Those who remained under satisfactory control without further surgery took medication for varying periods of time. One was under observation for less than 6 months, 3 were under observation for from 6 to 12 months, 6 were treated for from 1 to 2 years, 9 were under observation for from 2 to 4 years, and 12 were followed for from 4 to 7 years.

The duration of symptoms prior to the initiation of medication may have had some bearing on the success or failure of this form of management. Ten of the 13 (77%) who had had symptoms for less than one year were controlled on medication only, 14 of the 20 (70%) with symptoms from 2 to 5 years were controlled without surgery, 2 of the 7 (29%) with symptoms from 5 to 10 years were controlled with drugs alone and 6 of the 12 (50%) with symptoms for more than 10 years required further operative procedures for pain control.

The incidence of failure to control pain with drugs alone was not affected by age, previous surgical treatment or the presence of postoperative sensory deficit.

Many patients with pain control on medication reported painless paroxysmal paresthesiae similar to “Gasserian ghosts” described by Pennman. They described these with some difficulty using one or more of the following terms: prickle, tingle, pricking, throb, knock, quiver, jab, sparkle, touch, snap, twitch, flicker or bump. As their pain subsided during the first 2 weeks of treatment it was frequently replaced by these painless feelings, which occurred in the same distribution and had the same duration characteristic of their pain. They could, on occasion, be evoked from trigger points. Several patients came to consider recurrence of painless paroxysmal paresthesiae as a warning of an impending exacerbation of pain. Their medication was increased until the paresthesiae subsided.

Non-paroxysmal persistent paresthesiae were reported by 28 patients who described them as: sore gums or lips, crawling, burning, aching, stinging, pressure, gnawing, pinching, swollen cheek or lip, stiff lip or tongue, tingling and prickling or creeping. Seventeen had had previous operative procedures and 14 ultimately required another operative procedure for pain alleviation. The paresthesiae have persisted in each instance. Among the 11 who had not previously been operated upon, the paresthesiae were mild and intermittent. In no instance did they become a major problem in the patient’s management.

*Mephenesin Carbamate Suspension plus Diphenylhydantoin Sodium.* During acute exacerbations of pain, 20 patients were placed on supplemental diphenylhydantoin sodium, 100 mg., t.i.d. Twelve reported less pain after several days but were also taking larger doses of mephenesin at these times. Eight remained on continuing medication with both drugs for extended periods of time and felt more confident of having less pain in this circumstance. This group, however, is too small to compare the numbers requiring surgical intervention as compared to the whole group under observation.

*Intravenous Mephenesin.* An acute exacerbation of pain could be brought rapidly under full control by an adequately titrated dose of intravenous mephenesin. In the group of 20 patients thus treated, only 1 patient failed to report total alleviation of pain soon after the initiation of an adequate drip. This patient was an elderly amputee with severe emotional disturbance. He received a maximum intravenous dose of 4 gm. in 12 hours.
without evident side effects or relief. His complaints of pain and dysesthesia only gradually diminished after trigeminal rhizotomy.

**Side Effects of Mephenesine**

Mild side effects occurred frequently during the management of these patients. Many reported unsteadiness, light headedness, drowsiness, or mild nausea for 10 to 30 minutes after an oral dose of 3 gm. of mephenesin carbamate. These effects were transient and were reduced by taking the medication with milk or fruit juice. They diminished as the patient continued on medication. Three patients reported side effects but no pain relief on high doses of oral medication, although 2 of them were fully relieved of their pain during an intravenous drip.

Three patients developed a pale pink diffuse maculopapular rash of the trunk and extremities, which subsided despite continued use of the medication. In one other, the dermatitis was more severe and medication was discontinued temporarily.

Four patients reported that a golden blond tint developed in their scalp hair, eyebrows and eyelashes after prolonged use of the drug at high doses. In no instance was this a disturbing factor, although 3 of the 4 were women. All were brunettes. Two thought the change of hair color was most marked in the summer.

More striking side effects were seen in the patients who finally required operative intervention. The most common reason for interruption of the medical management of these patients was "dizziness", light-headedness and an unsteady gait without adequate pain control. These complaints were immediate precursors to operative intervention in 12 patients. Two patients had temperatures ranging from 102° to 104° and no satisfactory explanation for the fever was found. In one instance, the patient also had diverticulitis and diarrhea and it was not possible to implicate the medication alone. An abnormal temperature response to mephenesin has been reported in 3 instances.

**Mephenesin Plus Surgical Procedure**

Twenty-one patients required operative intervention, having remained controlled on medication prior to surgery for less than one month in 5 instances, 1 month to 12 months in 6 instances, 1 to 2 years in 8 instances, 2 to 3 years in 1 instance and 6 years in 1 instance. The vast majority of those requiring an operative procedure did so within 2 years (19 patients).

Six patients sought operative relief from other physicians during the period of these observations. In 5 instances the author was not available at the time of an acute exacerbation. In none of these 5 patients was the dosage of oral or intravenous medication changed in an attempt to control the acute exacerbation prior to operative intervention.

Factors suggesting social stress were prominent among the patients who came to operation. There were 6 who had marked anxiety and apprehension with any degree of discomfort or threat of discomfort. A profound language barrier in 4 required interpreters for communication. Occupational limitations required operative intervention after 5 days of initial observation in one patient. Two patients became psychotic following an operative procedure several weeks after medication was discontinued.

**Unusual Clinical Demonstrations**

*Seasonal Incidence of Exacerbations.* During the course of this study, we noted seasonal variation of the patients' symptoms. When clinical records clearly indicated an exacerbation of pain requiring an increased amount of medication, the incident was plotted according to the month of occurrence. All such certain episodes were tabulated on a twelve month graph (Fig. 1). Infections of the head and neck were frequently reported by patients before or during an exacerbation of pain but since we did know the incidence of these infections in an analogous control group, we did not feel justified in ascribing causal relationships. A similar tabulation of the operative procedures before and after medical management gave no evidence of seasonal variation.

*Special Sensory Testing.* Eight patients were selected for repeated testing of sensory thresholds with weighted pins and calibrated hairs. None had had previous operative procedures for their pain. None could identify any perceptible difference in sensation of the face when they were carefully tested in the usual clinical manner using a wisp of cotton or a hat pin. Seven, however, consistently reported altered sensibility when tested near
threshold for perception of touch or prick in those areas of the face affected by tic douloureux. Thresholds for light touch and pin "prick" were consistently elevated when compared to contralateral skin areas. Each patient reported a decrease in the perception of post-stimulation itch or tickle at threshold.

Examinations were performed while the patients were on both high and low doses of oral medication and when they were pain free or having only mild pain and paroxysmal dysesthesias. There was no evident change in these observations related to the dose of mephenesin carbamate.

Comment

Mephenesin carbamate suspension has been far more effective than other forms of mephenesin in the management of these patients. The elixir of mephenesin has less well sustained blood levels, although the initial absorption rate is similar. The tablet forms of mephenesin and mephenesin carbamate do not appear to maintain adequate blood levels unless unreasonable numbers of tablets are consumed.

Most patients with tic douloureux have symptomatic remissions which extend from weeks to many years. Spontaneous remissions exceeding 1 year have been rare in our group of patients although 2 reported that remissions in the past had exceeded 10 years. The immediate response to intravenous mephenesin, however, has been so consistent that there seems little likelihood that coincidental remissions have clouded the observation that the pain of tic douloureux ceases with an adequate blood level of mephenesin administered intravenously.

The efficacy of any form of continuing medical management of tic douloureux remains uncertain until it has been observed over an extended period of time. The observation that 19 of the 21 patients in the group who required an operative procedure did so within 2 years, has indicated that a trial period on medication beyond that time added little to the evaluation of its efficacy. The preliminary report noted a failure rate of 17% at the end of 1 year. The present series records a cumulative failure of 21% at 1 year, of 36% at 2 years and of 40% beyond.
2 years. While shorter periods of pain control occurred in many patients receiving mephenesin carbamate, the long term evaluation of their response to treatment must be considered in terms of a minimum of 2 years. Such extended periods of observation have rarely been the basis of clinical reports of the non-surgical management of patients with tic douloureux.

The observation that patients with a recent onset of symptoms required operative intervention less commonly (23%) than those with long-standing symptoms (66%) may indicate that a patient's tolerance for pain wanes with time or that the pain becomes more severe. No clear understanding of this observation has been established.20

A particular set of circumstances has evolved during this study which suggests that patients may be selectively chosen for this form of management. Those who have had tic douloureux for less than 5 years, who do not manifest inordinate anxiety or apprehension and who do not require an interpreter for communication have proven most likely to obtain so satisfactory a result that surgery was not necessary. In fact, 85% of the patients fulfilling these criteria have achieved satisfactory pain control without surgical intervention or serious side effects from the medication.

Kugelberg and Lindblom11 have suggested that the responses to sensory examination of trigger points indicates an altered central nervous system as the locus of the mechanism of the pain in tic douloureux. Slight alterations in sensory thresholds led Lewy and Grant14 to suggest that trigeminal neuralgia was a special form of thalamic syndrome. Our observations of altered responses to threshold sensory testing could be similarly interpreted. While speculation on the mechanism of pain in tic douloureux may be a fascinating exercise, more information defining the characteristics of normal and abnormal trigeminal somatosensory physiology are still essential before the problem of pain in tic douloureux can be solved.

Summary

We have observed 52 patients with tic douloureux over a period of 7 years. All were given mephenesin carbamate suspension to control their pain. Thirty-one (60%) maintained sufficient comfort to make a surgical procedure unnecessary. Patients with a short history of pain fared better than those with long-standing pain. A severe language barrier or marked anxiety adversely influenced their response to this form of long-term therapy.

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References


